Randomized Prospective Double-Blind Trial in Healing Chronic Diabetic Foot Ulcers

CT-102 activated platelet supernatant, topical versus placebo

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OBJECTIVE — To assess the efficacy of topically applied CT-102 APST for treating diabetic neurotrophic foot ulcers.

RESEARCH DESIGN AND METHODS — Thirteen patients entered a randomized, double-blind trial of topically applied CT-102 APST vs. placebo (normal saline) gauze dressings for the treatment of nonhealing diabetic neurotrophic foot ulcers. CT-102 APST (Curative Technologies, Setauket, NY) was prepared from homologous platelets and contained multiple growth factors including PDGF, PDAF, EGF, PF-4, TGF-β, aFGF, and bFGF. Inclusion criteria for subjects included diabetes, ulcer of >8 wk duration, peri-wound transcutaneous oxygen tension >30 mmHg, platelet count >100,000/mm^3, and no wound infection. Wounds were excised before entry and were >700 mm^3 but <50,000 mm^3 in volume, <100 cm^2 in area, and involved subcutaneous tissue.

RESULTS — In the CT-102 group, 5 of 7 ulcers were healed (100% epithelialized) by 15 wk, but only 1 of 6 ulcers was healed by 20 wk with placebo ($P < 0.05$). Average percent reduction in ulcer area at 20 wk was 94% for CT-102 vs. 73% for placebo. Daily reduction in ulcer volume was 73.8 ± 42.4 mm^3/day (mean ± SE) for CT-102 vs. 21.8 ± 8.1 mm^3/day for placebo ($P < 0.05$). Daily reduction in ulcer area was 6.2 ± 1.8 mm^2/day for CT-102 vs. 1.8 ± 0.4 mm^2/day for placebo ($P < 0.05$).

CONCLUSIONS — CT-102 significantly accelerated wound closure in diabetic leg ulcers when administered as part of a comprehensive program for the healing of chronic ulcers.

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RECEIVED FOR PUBLICATION 18 DECEMBER 1991 AND ACCEPTED IN REVISED FORM 9 APRIL 1992.

CT-102 APST, CT-102 ACTIVATED PLATELET SUPERNATANT, TOPICAL; PDGF, PLATELET-DERIVED GROWTH FACTOR; PDAF, PLATELET-DERIVED ANGIOGENESIS FACTOR; EGF, EPIDERMAL GROWTH FACTOR; PF-4, PLATELET FACTOR–4; TGF-B, TRANSFORMING GROWTH FACTOR-B; AFGF, ACIDIC FIBROBLAST GROWTH FACTOR; BFGF, BASIC FIBROBLAST GROWTH FACTOR; PDWHF, PLATELET DERIVED WOUND HEALING FORMULA, HOMOLOGOUS; ALT, ALANINE AMINOTRANSFERASE; HEPES, *N*-HYDROXYETHYLPIPERAZINE-*N*′-2-ETHANESULFONIC ACID; PB, HEPES BUFFER SOLUTION; CTAP-III, CONNECTIVE TISSUE-ACTIVATING PEPTIDE–III; PDECGF, PLATELET-DERIVED ENDOTHELIAL CELL GROWTH FACTOR; $TCPO_2$, TRANSCUTANEOUS OXYGEN TENSION; IDDM, INSULIN-DEPENDENT DIABETES MELLITUS.

The development of chronic, nonhealing cutaneous wounds is the result of inadequate tissue repair (1). Standard treatment of these nonhealing ulcers consists of use of antibiotics and protective dressings, resting the injured area, revascularization of ischemic limbs, and debridement of necrotic tissue. Repair of the wound occurs by new tissue ingrowth. Unfortunately, many ulcers respond poorly to conventional therapy, and chronic ulceration results.

An alternative approach is to apply platelet-derived growth factors directly to the wound surface to stimulate cellular movement, replication, and matrix synthesis and thus to transform a chronic nonhealing wound into a healing wound. Preparation of a platelet releasate containing several growth factors has been reported (1,2). To determine the effect on the healing of chronic diabetic neurotrophic foot ulcers by a topically applied purified platelet releasate, a randomized prospective double-blind study was undertaken.

RESEARCH DESIGN AND METHODS

— CT-102 APST, also known as Platelet Derived Wound Healing Formula, Homologous (PDWHF) was prepared from blood taken from a pool of pedigree donors participating in an Food and Drug Administration-licensed platelet apheresis program. The donors were screened for transmissible infectious diseases by history and physical examination and were tested directly for human immunodeficiency virus-type 1 (HIV-1), cytomegalovirus (CMV), human T-cell lymphotrophic virus-type 1 (HTLV-1), hepatitis B, and by surrogate tests (hepatitis B core antibody and serum ALT) for non-A, non-B hepatitis (now called hepatitis C), and syphilis. Each lot of CT-102 was made from a single donor to further reduce the possibility of transmitting infection. The CT-102 was prepared under aseptic conditions and supplied in sterile single-dose vials.

Each lot of CT-102 was prepared from platelets collected during apheresis with anticoagulant citrate dextrose and then cooled on ice. After a platelet count was performed, the platelets were removed from the platelet-rich plasma by centrifugation, and the platelet-poor plasma was discarded. The platelets were washed with a HEPES buffer solution and resuspended in PB at a concentration of 10^9 platelets/mm. The platelets then were stimulated to release the contents of α-granules with thrombin. The amount of thrombin in the final dilution of CT-102 was <0.005 U/ml. The spent platelets were removed by centrifugation and discarded. CT-102 then was diluted with buffer to a final concentration of 1:100.

The potency of CT-102 was monitored by the fibroblast mitogenic assay and the endothelial cell chemotaxis assay to determine that the factors in each releasate lot were active (3–5). The level of β-thromboglobulin also was determined for each lot using enzyme immunoassay kits obtained from American Bioproducts (Parsipanny, NJ). Analysis of retained lot samples were tested for PDGF, TGF-β, and PF-4. No significant differences were observed in lot-to-lot consistency. CT-102 was prepared and supplied by Curative Technologies at no charge to patients. All ulcer care was supplied free during the trial.

No assays were performed on the platelet-poor plasma and HEPES washes for the lots of material prepared for this study. Separate studies of β-thromboglobulin, albumin, and total protein on the platelet-poor plasma and the subsequent washes of the platelets demonstrated that there is no spontaneous release of the α-granules during this procedure, and that plasma protein has been eliminated by the third wash of the platelets.

All patients entered into the trial were seen at the Wound Healing/Limb Preservation Clinic at the University of Pittsburgh or at the Wound Clinic at the Maricopa Medical Center in 1989. These patients were referred to the clinic because their wounds had not healed under the care of their personal physicians. This trial was a pilot phase of an expanded multidilution trial of CT-102. Institutional Review Board approval was obtained before beginning the study.

Patients were screened for the trial by an initial history and physical examination. Patients selected for the trial had a neurotrophic ulcer of the lower extremity that had not healed after at least 8 wk of standard treatment. Only patients with diabetes mellitus were studied. All patients had a platelet count ≥100,000/mm^3. Only patients with a supine periwound $TcPO_2$ >30 mmHg were accepted. All patients were evaluated for infection in the wound with plain radiographs before debridement. We understood that the early stages of osteomyelitis might not appear on plain radiographs and that the definitive determination of osteomyelitis would be made at debridement. No patient with clinical signs of infection such as erythema, induration, tenderness, fever, or chills was entered into the trial. Wounds were not cultured, and no patient was entered if they required antibiotic therapy.

Aggressive debridement to essentially excise the wound was performed before entry into the trial. Debridements were performed in an outpatient operating room under regional block anesthesia. The ulcer and surrounding callus were completely excised down to normal uninvolved tissue. All ulcers were >700 mm^3 in volume but <50,000 mm^3. Wounds were less than 100 cm^2 in area.

Patients were evaluated each week for 3 wk and then every other week until the wound was completely healed or the patient completed 20 wk of treatment. The length, width, and depth of the ulcers were measured and the ulcers were photographed at each visit. Ulcers were rated according to functional assessment at entry into the trial and at each visit against the following scale: level 1, <100% epithelialized, drainage present, dressing needed; level 2, 100% epithelialized, much drainage present, dressing needed; level 3, 100% epithelialized, no or minimal drainage, only protective dressing needed; and level 4, 100% epithelialized, mature skin present, no dressing needed.

All subjects were treated as outpatients. All patients agreed to be totally non–weight-bearing. Patients were supplied with a half-shoe (IPOS North American, Niagara Falls, NY) that transferred weight to their heel and could be used for balance. Patients used wheelchairs, crutches, or walkers to avoid weight-bearing. Compliance was assessed by direct questioning of the patient and family. Also, any patient who walked into the clinic during the trial was considered to be weight-bearing at home.

Each patient or a family member changed the ulcer dressing every 12 h. Either CT-102 or placebo (normal saline) was applied to a cotton gauze sponge and placed on the ulcer in the evening. The CT-102 and placebo solutions were identical in appearance. Neither the investigators nor the patients were able to distinguish between the two products. Normal saline was chosen as the treatment for the control group because it is the standard dressing for diabetic foot ulcers at the clinic. The CT-102- or placebo-soaked gauze was covered with petrolatum-impregnated gauze to keep the area moist. The following morning, the dressing was removed. All patients applied a normal saline cotton gauze to the wound for the next 12 h.

Data for each group were arranged at each visit interval, and the two groups were compared by Wilcoxon's matched-pairs test. This test compares two sets of data that are scored in an ordered classification. The samples are arranged in a rank order. The average ranks are compared in that ordering. Data for reduction in ulcer volume and area was evaluated for statistical significance using Student's paired *t* test.

RESULTS — Thirteen patients (9 men, 4 women) were entered into the trial (Table 1). The 7 patients in the CT-102

Table 1—*Comparison of baseline characteristics of CT-102- vs. placebo-treated patients*

Characteristic	CT-102 APST	Placebo	*P* value
Age (yr)	58.7 ± 12.4	54.2 ± 12.9	0.5316
Sex			0.6547
Male	5	4	
Female	2	2	
Duration of diabetes mellitus (yr)	26 ± 6.6	10.3 ± 5.9	0.001
$TCPO_2$ (mmHg)	51 ± 8.4	45 ± 7.4	0.6452
HbA_{1C} (%)	7.1 ± 1.4	7.5 ± 1.4	0.5272
Transferrin (mg/dl)	254.3 ± 32.8	274.3 ± 67.2	0.4793

Values are means ± SD.

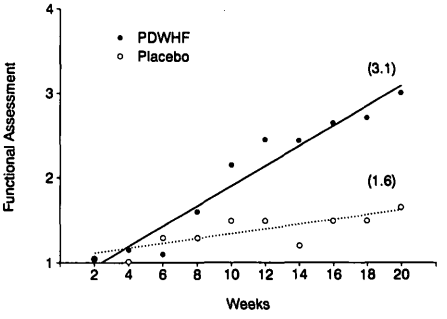

Figure 1—*Functional assessment of each wound was measured at each visit and is plotted vs. wk of treatment ($P < 0.02$).*

group were 39–75 yr of age with a mean of 59 yr. The 6 patients in the placebo group were 41–74 yr of age with a mean of 54 yr. Ulcer duration before treatment was 17 mo for the CT-102 group (range 4–48 mo) and 13 mo for the placebo group (range 3–42 mo; Table 2). Ulcers were characterized at entry into the trial. All ulcers in the placebo group and 6 of 7 ulcers in the CT-102 group were full-thickness ulcers extending into the subcutaneous tissue. All ulcers were on the plantar surface of the distal half of the foot beneath a metatarsal head with the exception of one ulcer located over the lateral malleolus. One patient in the CT-102 group had a deeper ulcer of the plantar surface extending into the tendon and bone, and requiring debridement.

In patients treated with CT-102, 5 of 7 ulcers healed by 15 wk—defined as achieving functional status level 3 or 4. Only 1 of 6 ulcers healed by 20 wk in the placebo group (Table 3, Fig. 1). There was no relationship between ulcer duration or initial size and healing. The average portion of area healed at 20 wk in the CT-102 group was 94%, whereas in the placebo group it was 73% ($P < 0.02$; Fig. 2). One of the 2 patients not healed at 20 wk in the CT-102 group was found to have underlying osteomyelitis. Upon review, this appeared to be present at entry into the trial and may help to explain the lack of healing in this patient. The other CT-102–treated patient achieved functional level 2.

Four of the patients who received placebo treatment entered a compassionate-use study and received CT-102; 3 patients went on to complete healing, while the 4th patient had >90% healing of their ulcers within 20 wk.

The area and volume of the ulcers were calculated for each ulcer at each visit. The average daily reduction in ulcer volume was 73.8 ± 112.2 mm^3 (mean ± SD) for the CT-102 group vs. 21.8 ± 19.9 mm^3 for the placebo group (Table 4; $P < 0.05$). The percentage of volume healed was not linear with time; rather, the percent volume healed increased rapidly at first, then slowed with time. The percentage of volume healed was plotted versus the weeks of treatment (Fig. 3). Regression analysis was performed on the percentage of ulcer volume healed on the day of each clinic visit for each patient. The percentage of volume healed was transformed by the function −ln (101 − % volume healed/101). The number 101 was used instead

Table 2—*Wound duration before treatment*

PDWHF group		Placebo group	
Duration (mo)	Wounds (*n*)	Duration (mo)	Wounds (*n*)
4.5	1	3.0	1
6.0	2	7.5	1
13.0	1	8.0	1
15.0	1	8.5	1
16.0	1	9.0	1
48.0	1	42.0	1
Total wounds	7		6
Mean duration (mo)	17.08		13.00
SD (mo)	15.87		14.37

Table 3—*Functional assessment after 20 wk of treatment*

	PDWHF patients	Placebo patients
Level 1: <100% epithelized; with drainage	1	3
Level 2: epithelized 100% with drainage, needs dressing	1	2
Level 3: epithelized 100%; maturing skin with small amount of drainage	2	1
Level 4: epithelized 100%; 100% mature skin; dressing not needed	3	0
Total wounds	7	6

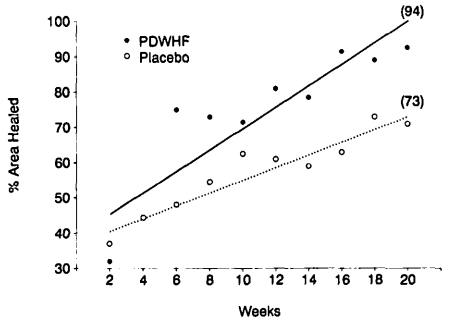

Figure 2—*Percent area healed was measured at each visit and is plotted vs. wk of treatment ($P < 0.02$).*

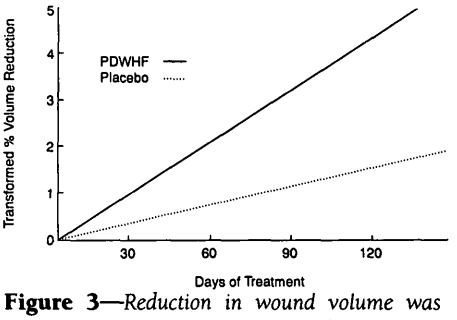

Figure 3—*Reduction in wound volume was measured at each visit and transformed by function $-ln$ ([101 − percent volume healed]/101). Transformed percent volume reduction is plotted vs. days of treatment.*

of 100 to avoid taking the logarithm of 0. The average slope of the transformed percentage in volume reduction represented the rate of healing. The average slopes of the transformed percentage in volume reduction was compared between the two groups. The average for CT-102 was 0.0364 ± 0.0100 mm^3 (mean ± SE). For placebo, the slope was 0.0143 ± 0.0057 mm^3. The rate of ulcer healing was significantly better for CT-102 than placebo ($P < 0.05$).

A similar analysis was performed on the area healed or the percentage of area reduction (Table 5, Fig. 4). The average daily reduction in the ulcer area was 6.2 ± 4.8 mm^2/day (mean ± SD) for CT-102 vs. 1.8 ± 1.1 mm^2/day for placebo. The same transformation was made on the percentage of area healed as was made on the percentage of volume healed, and a model was fit in the same manner (Fig. 4). The average slope for the CT-102 group was 0.0347 ± 0.0097 mm^2 (mean ± SE) and 0.0110 ± 0.0039 mm^2 for the placebo group. The results demonstrated a greater rate of reduction in the ulcer area for CT-102 compared with placebo ($P < 0.03$).

CONCLUSIONS— Chronic nonhealing cutaneous ulcers of the lower extremity affect millions of patients each year. A variety of etiologies account for these ulcers, including arterial insufficiency, chronic venous insufficiency, pressure, vasculitis, malignancy, and radiation necrosis. Common reasons for the failure of ulcers to heal include infection and poor tissue perfusion. These factors may prevent new tissue growth, resulting in a nonhealing wound. Histological examination of these wounds demonstrates very poor cellularity, few fibroblasts, few new capillaries, and few inflammatory cells. In contrast, healing wounds are characterized by a mononuclear and macrophage cellular infiltrate, dividing fibroblasts, and numerous capillaries.

Wound healing is a complex process involving many different factors. With injury, a series of serum enzyme cascades are activated, which then initiate the healing process. The coagulation cascade controls hemorrhage in the wound space. The same factors that activate the coagulation cascade also activate the fibrinolytic system, which modulates the coagulation process. The complement cascade is similarly activated, resulting in formation of C5A, which is a chemoattractant for neutrophils. In addition, activation of the kinin cascade results in formation of potent vasodilators that bring blood and other healing factors into the wound.

These serum enzyme cascades interact with the local environment and result in several different cells being brought into the wound including platelets, monocytes, macrophages, fibroblasts, and epithelial and endothelial cells. The wound environment is regu-

Table 4—*Daily wound volume*

No.	Initial volume (mm^3)	Final volume (mm^3)	Reduction (mm^3)	Days to final volume	Daily reduction (mm^3/day)
CT-102 patients					
1	22,275	0	22,275	70	318.2
2	3840	0	3840	140	27.4
3	5184	4816	368	98	3.8
4	5200	0	5200	140	37.1
5	1470	0	1470	79	18.6
6	10,752	0	10,752	109	98.6
7	2975	1188	1787	140	12.8
Mean	7385.1	857.7			73.8
SD	7184.1	1800.7			112.2
Placebo patients					
1	2250	936	1314	140	9.38
2	770	4840	0	70	0
3	7038	1	7037	142	49.5
4	714	0	714	143	4.9
5	6825	1430	5395	143	37.7
6	8750	4500	4250	146	29.1
Mean	4391.2	1951.2			21.8
SD	3553.8	2179.6			19.9

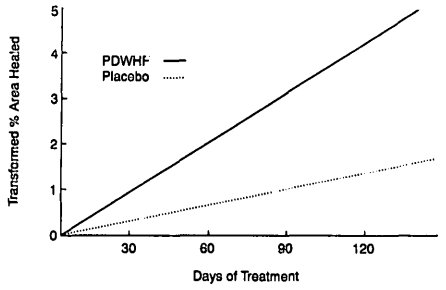

Figure 4—*Reduction in wound area was measured at each visit and transformed by function −ln ([101 − percent area healed]/101). Transformed percent area reduction is plotted vs. days of treatment.*

lated by platelet products during the first 24 h of healing and thereafter by the monocyte, which becomes a wound macrophage influencing conditions in the wound until healing is complete. The platelets and subsequently the macrophages release growth factors into the wound. These growth factors are polypeptides that regulate the growth, differentiation, and metabolism of cells, serving as mitogens and chemoattractants to promote wound healing. The growth factors are chemoattractants for neutrophils and monocytes, stimulate fibroblast migration and proliferation, and lead to collagen synthesis and deposition. These growth factors also serve as endothelial and epithelial cell chemoattractants and mitogens.

Various growth factors have been isolated from human platelets. These include PDGF, PDAF, EGF, TGF-α, TGF-β, PF-4, β-thromboglobulin, CTAP-III, PDECGF, and aFGF and bFGF.

PDGF is a well-characterized 30,000 M_r dimeric glycoprotein and is a known fibroblast and monocyte chemoattractant (6,7). In addition, PDGF stimulates the replication of a variety of cells including fibroblasts.

PDAF is a protein of ~8,000-M_r that stimulates chemotaxis of capillary and other endothelial cells (8). EGF and TGF-α are proteins known to be chemoattractants and mitotic factors for keratinocytes (9). PF-4 is a chemoattractant for neutrophils and monocytes (10). TGF-β is 25,000-M_r polypeptide that increases the synthesis of collagen through the stimulation of macrophages and fibroblasts. TGF-β is also involved in the control of angiogenesis (11,12).

CTAP-III is a 9,000 M_r single-chain protein that is chemotactic for fibroblasts. β-thromboglobulin has the same sequence as CTAP-III except that the first four amino acids are deleted (13,14). PDECGF is a 45,000-M_r protein that stimulates endothelial cell mitogenesis (15). Both aFGF and bFGF have been reported in platelets. FGF is a potent mitogen and chemotactic agent for mesodermal and endothelial cells (16).

The wound environment is regulated by growth factors released from platelets in the first 24 h after injury and thereafter by macrophages. Growth factors bind to specific membrane receptors, resulting in a series of events and biochemical changes leading to DNA synthesis and cellular division, as well as synthesis of extracellular matrix proteins such as collagen and proteoglycans. Modulation of growth factor activity is not completely understood but includes changes in anchorage dependence of cells and competition for cellular receptors.

Previous work with autologous PDWHF has suggested that it is of benefit in healing of chronic wounds. Knighton et al. (1) reported on the treatment of 49 patients with chronic nonhealing wounds using PDWHF prepared autologously from blood harvested from the patient (1). Autologous PDWHF was diluted with microcrystalline collagen. A variety of wounds were treated under an open label. His study showed a direct correlation between wound healing and the initiation of PDWHF therapy. No abnormal tissue formation, keloid, or hypertrophic scarring was seen in patients treated in this fashion.

Another study by Doucette et al. (17) was performed on patients referred to the University of Minnesota Wound Healing and Limb Salvage Clinic for am-

Table 5—*Daily wound area*

No.	Initial area (mm^2)	Final area (mm^2)	Reduction (mm^2)	Days to final area	Daily reduction (mm^2/day)
CT-102 patients					
1	825	0	825	70	11.8
2	480	0	480	140	3.4
3	1296	1204	92	98	0.9
4	1300	0	1300	140	9.3
5	210	0	210	79	2.7
6	1344	0	1344	109	12.3
7	595	198	397	140	2.8
Mean	864.3	200.3			6.2
SD	457.6	448.7			4.8
Placebo patients					
1	375	140	235	140	1.7
2	154	440	0	70	0
3	306	1	305	142	2.2
4	238	49	189	143	1.3
5	525	143	382	143	2.7
6	875	450	425	146	2.9
Mean	412.2	206.5			1.8
SD	259.5	193.6			1.1

putation. With the comprehensive wound-care program, including use of autologous PDWHF, successful wound healing was reported in 84% of patients.

Knighton et al. (2) reported a randomized prospective double-blind trial comparing autologous PDWHF diluted in collagen versus a control solution of microcrystalline collagen in platelet buffer in the healing of lower extremity wounds of various etiologies. Thirteen patients with 21 wounds were treated with PDWHF; 17 of 21 wounds healed to 100% epithelialization after 8 wk of therapy; of 11 patients with 13 wounds in the placebo group, only 2 of 13 wounds achieved 100% epithelization. Our study of homologous platelet derived growth factors differed from Knighton's study in that he used an autologous preparation, although the methodology of deriving the growth factors was similar. In addition, the endpoints in our study were more stringent in that the wound volume and area reduction were evaluated in addition to healing to functional skin compared with achievement of 100% epithelialization in the Knighton studies.

Atri et al. (18) reported the use of homologous platelet factors in achieving total healing of recalcitrant skin ulcers in 23 patients. In this study, each ulcer acted as its own control. During a 3-mo control period, only 3 ulcers in 3 patients completely healed. However, with homologous PDWHF, the remaining 24 ulcers in 20 patients achieved 100% healing in 9.7 wk. Age, sex, location of ulcer, ulcer duration, and ulcer size had no influence on PDWHF-stimulated rates of healing. These results are the most favorable published at this time.

Studies of individual platelet factors suggested enhancement of wound healing as well. A randomized prospective double-blind trial of EGF/Silvadene versus Silvadene in the treatment of skin-graft donor sites showed a statistically significant but clinically unimportant improvement in healing with EGF (19).

Our trial was a randomized prospective double-blind study and was restricted to patients with diabetes. Patients had diabetic neurotrophic ulcers that had been present for an average 13 mo in the control group and 17 mo in the treatment group. All patients had $TCPO_2$ measured on the dorsum of the foot. $TCPO_2$ >30 mmHg was used as an entry criterion for the trial. Poor ulcer healing has been associated with $TCPO_2$ levels <20–40 mmHg (20–22). A $TCPO_2$ of 30 mmHg was chosen as a midrange level suggesting adequate oxygenation for ulcer healing to occur. Patients were evaluated with Doppler arterial pressures and wave forms, but we recognized that segmental pressures may be elevated falsely in diabetic patients, who often have calcification of the media of the arterial wall.

Analysis of the data demonstrated a significant improvement in ulcer healing in patients treated with CT-102 compared with patients treated with placebo. Five of 7 patients treated with CT-102 achieved a functional assessment of level 3 or 4 by 15 wk of treatment, whereas only 1 of 6 patients healed when treated with placebo. There was a statistically significant difference in reduction in ulcer area between the two groups. A 94% reduction in area in patients treated with CT-102 was achieved versus a 73% reduction in ulcer area in patients treated with placebo. However, these chronic ulcers were present for 3–48 mo (mean >13 mo) without healing, and yet there was a significant reduction in ulcer size even in the control group treated with placebo. This emphasizes the important contribution of an aggressive program of ulcer care. Patients who participate in a multidisciplinary wound-care program benefit from good care even when saline dressings are used.

Patients underwent wide debridement of all ulcer tissue before entry into the study. It is our impression that vigorous debridement as can only be performed in the operating room under regional anesthesia played a significant role in ulcer healing in both the CT-102 and the placebo groups. Also, all patients were prohibited from weight-bearing on the ulcer and were strictly admonished to stay off their feet as much as possible. Patients who were seen walking in the clinic were cautioned about weight-bearing. It was assumed that if they were nonweight-bearing at home, they would do the same at their clinic visit. Compliance was thought to be equal in the two groups. While on their feet, the subjects wore a postoperative shoe to redistribute weight to their heel and away from the ulcer. All patients in both groups were supplied with these shoes. These, too, played a role in the improvement in these ulcers. However, we emphasize that although both the CT-102- and placebo-treated patients had a reduction in ulcer volume and area, the CT-102 group healed statistically significantly faster and more completely than the placebo group.

In summary, the results from this trial demonstrate a significantly enhanced clinical response in patients with diabetic neurotrophic ulcers treated with CT-102 compared with placebo. CT-102 appears to play a dominant role in the healing progress when administered as part of a comprehensive program for the healing of a chronic ulcer.

Acknowledgments— This research was supported in part by Curative Technologies, Inc., Setauket, New York.

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